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1. Your reference 101418-1

2. Patent application number *(The Patent Office will fill in this part)* 0406446.5

23 MAR 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation: Sweden

4. Title of the invention

COMBINATION THERAPY

5. Name of your agent *(if you have one)*

Tracy Anne BURNS

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
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P O Box 272
Mereside, Alderley Park
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Signature S. A. Douglas Date 22/03/2004

12. Name and daytime telephone number of person to contact in the United Kingdom: Mrs Shirley A Douglas - 01625 510057

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COMBINATION THERAPY

The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which is optionally being treated with ionising radiation, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises one of: the administration of AZD2171 in combination with 5-FU; the administration of AZD2171 in combination with CPT-11; and the administration of AZD2171 in combination with 5-FU and CPT-11; to a pharmaceutical composition comprising one of: AZD2171 and 5-FU; AZD2171 and CPT-11; and AZD2171 and 5-FU and CPT-11; to a combination product comprising one of: AZD2171 and 5-FU; AZD2171 and CPT-11; and AZD2171 and 5-FU and CPT-11, for use in a method of treatment of a human or animal body by therapy; to a kit comprising one of: AZD2171 and 5-FU; AZD2171 and CPT-11; and AZD2171 and 5-FU and CPT-11; to the use of one of: AZD2171 and 5-FU; AZD2171 and CPT-11; and AZD2171 and 5-FU and CPT-11, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J.

Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844).

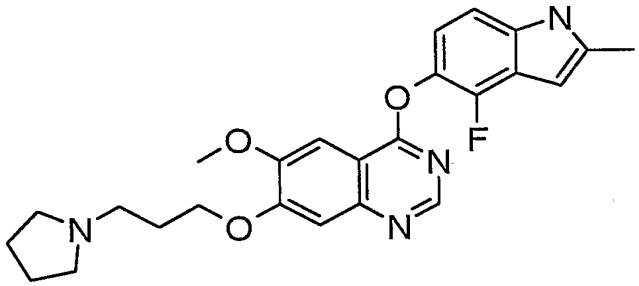
Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt-1 (also referred to as VEGFR-1), the kinase insert domain-containing receptor, KDR (also referred to as VEGFR-2 or Flk-1), and another fms-like tyrosine kinase receptor, Flt-4. Two of these related RTKs, Flt-1 and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

VEGF is a key stimulus for vasculogenesis and angiogenesis. This cytokine induces a vascular sprouting phenotype by inducing endothelial cell proliferation, protease expression and migration, and subsequent organisation of cells to form a capillary tube (Keck, P.J., Hauser, S.D., Krivi, G., Sanzo, K., Warren, T., Feder, J., and Connolly, D.T., Science (Washington DC), *246*: 1309-1312, 1989; Lamoreaux, W.J., Fitzgerald, M.E., Reiner, A., Hasty, K.A., and Charles, S.T., Microvasc. Res., *55*: 29-42, 1998; Pepper, M.S., Montesano, R., Mandroita, S.J., Orci, L. and Vassalli, J.D., Enzyme Protein, *49*: 138-162, 1996.). In addition, VEGF induces significant vascular permeability (Dvorak, H.F., Detmar, M., Claffey, K.P., Nagy, J.A., van de Water, L., and Senger, D.R., (Int. Arch. Allergy Immunol., *107*: 233-235, 1995; Bates, D.O., Heald, R.I., Curry, F.E. and Williams, B. J. Physiol. (Lond.), *533*: 263-272, 2001), promoting formation of a hyper-permeable, immature vascular network which is characteristic of pathological angiogenesis.

It has been shown that activation of KDR alone is sufficient to promote all of the major phenotypic responses to VEGF, including endothelial cell proliferation, migration, and survival,

and the induction of vascular permeability (Meyer, M., Clauss, M., Lepple-Wienhues, A., Waltenberger, J., Augustin, H.G., Ziche, M., Lanz, C., Büttner, M., Rziha, H-J., and Dehio, C., EMBO J., *18*: 363-374, 1999; Zeng, H., Sanyal, S. and Mukhopadhyay, D., J. Biol. Chem., *276*: 32714-32719, 2001; Gille, H., Kowalski, J., Li, B., LeCouter, J., Moffat, B, Zioncheck, T.F., Pelletier, N. and Ferrara, N., J. Biol. Chem., *276*: 3222-3230, 2001).

Quinazoline derivatives which are inhibitors of VEGF receptor tyrosine kinase are described in International Patent Application Publication No. WO 00/47212. AZD2171 is described in WO 00/47212 and is Example 240 therein. AZD2171 is 4-(4-fluoro-2-methyl-1*H*-indol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline:



AZD2171

AZD2171 shows excellent activity in the *in vitro* (a) enzyme and (b) HUVEC assays that are described in WO 00/47212 (pages 80-83). The AZD2171 IC_{50} values for inhibition of isolated KDR (VEGFR-2) and Flt-1 (VEGFR-1) tyrosine kinase activities in the enzyme assay were <2 nM and 5 ± 2 nM respectively. AZD2171 inhibits VEGF-stimulated endothelial cell proliferation potently (IC_{50} value of 0.4 ± 0.2 nM in the HUVEC assay), but does not inhibit basal endothelial cell proliferation appreciably at a > 1250 fold greater concentration (IC_{50} value is > 500 nM). The growth of a Calu-6 tumour xenograft in the *in vivo* solid tumour model described in WO 00/47212 (page 83) was inhibited by 49%**, 69%*** and 91%*** following 28 days of once-daily oral treatment with 1.5, 3 and 6 mg/kg/day AZD2171 respectively ($P^{**}<0.01$, $P^{***}<0.0001$; one-tailed t test). AZD2171 has been shown to elicit broad-spectrum anti-tumour activity in a range of models following once-daily oral administration.

In WO 00/47212 it is stated that compounds of the invention:

"may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment."

WO 00/47212 then goes on to describe examples of such conjoint treatment including surgery, radiotherapy and various types of chemotherapeutic agent including 5-fluorouracil (5-FU) and irinotecan (CPT-11).

Nowhere in WO 00/47212 is a specific combination of AZD2171 and CPT-11 and/or 5-FU suggested.

Nowhere in WO 00/47212 does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects.

Unexpectedly and surprisingly we have now found that the particular compound AZD2171 used in combination with a particular selection of combination therapies, namely with one of: 5-FU; CPT-11; and 5-FU and CPT-11, produces significantly better antiangiogenic and/or vascular permeability reducing effects than any one of: AZD2171; 5-FU; CPT-11; and 5-FU and CPT-11 used alone. According to one aspect of the present invention, AZD2171 used in combination with one of: 5-FU; CPT-11; and 5-FU and CPT-11 produces significantly better anti-cancer effects than any one of: AZD2171; 5-FU; CPT-11; and 5-FU and CPT-11 used alone. According to one aspect of the present invention, AZD2171 used in combination with one of: 5-FU; CPT-11; and 5-FU and CPT-11 produces significantly better effects on solid tumours than any one of: AZD2171; 5-FU; CPT-11; and 5-FU and CPT-11 used alone. According to one aspect of the present invention, AZD2171 used in combination with one of: 5-FU; CPT-11; and 5-FU and CPT-11 produces significantly better effects in colorectal cancer than any one of: AZD2171; 5-FU; CPT-11; and 5-FU and CPT-11 used alone.

Anti-cancer effects of a method of treatment of the present invention include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present invention include, but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. It is expected that when a method of treatment of the present

invention is administered to a warm-blooded animal such as a human, in need of treatment for cancer, with or without a solid tumour, said method of treatment will produce an effect, as measured by, for example, one or more of: the extent of the anti-tumour effect, the response rate, the time to disease progression and the survival rate. Anti-cancer effects include prophylactic treatment as well as treatment of existing disease.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of one of:

a) 5-FU;

b) CPT-11; and

c) 5-FU and CPT-11.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of one of: 5-FU; CPT-11; and 5-FU and CPT-11.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of one of: 5-FU; CPT-11; and 5-FU and CPT-11.

According to a further aspect of the present invention there is provided a method for the treatment of colorectal cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of one of: 5-FU; CPT-11; and 5-FU and CPT-11.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or

simultaneously with an effective amount of one of: 5-FU; CPT-11; and 5-FU and CPT-11; wherein AZD2171, 5-FU and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of one of: 5-FU; CPT-11; and 5-FU and CPT-11; wherein AZD2171, 5-FU and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of one of: 5-FU; CPT-11; and 5-FU and CPT-11; wherein AZD2171, 5-FU and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of colorectal cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of one of: 5-FU; CPT-11; and 5-FU and CPT-11; wherein AZD2171, 5-FU and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises AZD2171 or a pharmaceutically acceptable salt thereof, and 5-FU in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises AZD2171 or a pharmaceutically acceptable salt thereof, and CPT-11 in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises AZD2171 or a pharmaceutically acceptable salt thereof, and 5-FU and CPT-11 in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a combination product comprising AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU, for use in a method of treatment of a human or animal body by therapy.

According to a further aspect of the present invention there is provided a combination product comprising AZD2171 or a pharmaceutically acceptable salt thereof and CPT-11, for use in a method of treatment of a human or animal body by therapy.

According to a further aspect of the present invention there is provided a combination product comprising AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU and CPT-11, for use in a method of treatment of a human or animal body by therapy.

According to a further aspect of the present invention there is provided a kit comprising AZD2171 or a pharmaceutically acceptable salt thereof, and 5-FU.

According to a further aspect of the present invention there is provided a kit comprising AZD2171 or a pharmaceutically acceptable salt thereof, and CPT-11.

According to a further aspect of the present invention there is provided a kit comprising AZD2171 or a pharmaceutically acceptable salt thereof, and 5-FU and CPT-11.

According to a further aspect of the present invention there is provided a kit comprising:

a) AZD2171 or a pharmaceutically acceptable salt thereof in a first unit dosage form;

b) 5-FU in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) AZD2171 or a pharmaceutically acceptable salt thereof in a first unit dosage form;

b) CPT-11 in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) AZD2171 or a pharmaceutically acceptable salt thereof in a first unit dosage form;

b) 5-FU in a second unit dosage form;

c) CPT-11 in a third unit dosage form; and

d) container means for containing said first, second and third dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) AZD2171 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient or carrier, in a first unit dosage form;

b) 5-FU together with a pharmaceutically acceptable excipient or carrier, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) AZD2171 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient or carrier, in a first unit dosage form;

b) CPT-11 together with a pharmaceutically acceptable excipient or carrier, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) AZD2171 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient or carrier, in a first unit dosage form;

b) 5-FU together with a pharmaceutically acceptable excipient or carrier, in a second unit dosage form;

c) CPT-11 together with a pharmaceutically acceptable excipient or carrier, in a third unit dosage form; and

d) container means for containing said first, second and third dosage forms.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and one of:

a) 5-FU;

b) CPT-11; and

c) 5-FU and CPT-11

in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and one of:

a) 5-FU;

b) CPT-11; and

c) 5-FU and CPT-11

in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and one of:

a) 5-FU;

b) CPT-11; and

c) 5-FU and CPT-11

in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and one of:

a) 5-FU;

b) CPT-11; and

c) 5-FU and CPT-11

in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human wherein the cancer is a colorectal cancer.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of 5-FU, optionally together with a pharmaceutically acceptable excipient or carrier, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the AZD2171 and 5-FU may be administered simultaneously, sequentially or separately and in any order.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of CPT-11, optionally together with a pharmaceutically acceptable excipient or carrier, to a warm-blooded

animal such as a human in need of such therapeutic treatment wherein the AZD2171 and CPT-11 may be administered simultaneously, sequentially or separately and in any order.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of 5-FU, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of CPT-11, optionally together with a pharmaceutically acceptable excipient or carrier, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the AZD2171, 5-FU and CPT-11 may be administered simultaneously, sequentially or separately and in any order.

A combination treatment of the present invention as defined herein may be achieved by way of the simultaneous, sequential or separate administration of the individual components of said treatment. A combination treatment as defined herein may be applied as a sole therapy or may involve surgery or radiotherapy or an additional chemotherapeutic agent in addition to a combination treatment of the invention. Surgery may comprise the step of partial or complete tumour resection, prior to, during or after the administration of the combination treatment with AZD2171 described herein.

Other chemotherapeutic agents for optional use with a combination treatment of the present invention include those described in WO 00/47212 which is incorporated herein by reference. Such chemotherapy may cover five main categories of therapeutic agent:

(i) other antiangiogenic agents including vascular targeting agents;

(ii) cytostatic agents;

(iii) biological response modifiers (for example interferon);

(iv) antibodies (for example edrecolomab); and

(v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology; and other categories of agent are:

(vi) antisense therapies;

(vii) gene therapy approaches; and

(ix) immunotherapy approaches.

Particular examples of chemotherapeutic agents for use with a combination treatment of the present invention are raltitrexed, etoposide, vinorelbine, paclitaxel, docetaxel, cisplatin,

oxaliplatin, gemcitabine; such combinations are expected to be particularly useful for the treatment of cancer of the lung, head and neck, colon, rectum, oesophagus, stomach, cervix, ovary, skin, breast, bladder and pancreas.

The administration of a multiple combination of AZD2171, 5-FU and ionising radiation or AZD2171, CPT-11 and ionising radiation or AZD2171, 5-FU, CPT-11 and ionising radiation may produce effects, such as anti-tumour effects, greater than those achieved with any of AZD2171, 5-FU, CPT-11 and ionising radiation used alone. The administration of a multiple combination of AZD2171, 5-FU and ionising radiation or AZD2171, CPT-11 and ionising radiation or AZD2171, 5-FU, CPT-11 and ionising radiation may produce effects, such as anti-tumour effects, greater than those achieved with the combination of AZD2171 and 5-FU, greater than those achieved with the combination of AZD2171 and CPT-11 and greater than those achieved with the combination of AZD2171, 5-FU and CPT-11. The administration of a multiple combination of AZD2171, 5-FU and ionising radiation or AZD2171, CPT-11 and ionising radiation or AZD2171, 5-FU, CPT-11 and ionising radiation may produce effects, such as anti-tumour effects, greater than those achieved with the combination of AZD2171 and ionising radiation, greater than those achieved with the combination of 5-FU and ionising radiation, greater than those achieved with the combination of CPT-11 and ionising radiation, and greater than those achieved with the combination of 5-FU, CPT-11 and ionising radiation.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU and before, after or simultaneously with an effective amount of ionising radiation.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a

human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation.

According to the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU and before, after or simultaneously with an effective amount of ionising radiation.

According to the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation.

According to the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation.

According to the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU and before, after or simultaneously with an effective amount of ionising radiation.

According to the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation.

According to the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises

administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation.

In particular the cancer involving a solid tumour is colorectal cancer.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and 5-FU may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171, 5-FU and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and 5-FU

may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171, 5-FU and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and 5-FU may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171 and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human,

which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of 5-FU, before, after or simultaneously with an effective amount of CPT-11 and before, after or simultaneously with an effective amount of ionising radiation, wherein AZD2171, 5-FU and CPT-11 may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

In particular the warm-blooded animal such as a human has colorectal cancer.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and CPT-11 in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU and CPT-11 in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and CPT-11 in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU and CPT-11 in the

manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

In particular the warm-blooded animal such as a human has colorectal cancer.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and CPT-11 in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU and CPT-11 in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of 5-FU, optionally together with a pharmaceutically acceptable excipient or carrier and the administration of an effective amount of ionising radiation, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the AZD2171, 5-FU and ionising radiation may be administered simultaneously, sequentially or separately and in any order.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of CPT-11, optionally together with a pharmaceutically acceptable excipient or carrier and the administration of an effective amount of ionising radiation, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the AZD2171, CPT-11 and ionising radiation may be administered simultaneously, sequentially or separately and in any order.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of 5-FU, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of CPT-11, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of ionising radiation, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the AZD2171, 5-FU, CPT-11 and ionising radiation may be administered simultaneously, sequentially or separately and in any order.

A warm-blooded animal such as a human which is being treated with ionising radiation means a warm-blooded animal such as a human which is treated with ionising radiation before, after or at the same time as the administration of a medicament or combination treatment comprising AZD2171 and one of: 5-FU; CPT-11; and 5-FU and CPT-11. For example said ionising radiation may be given to said warm-blooded animal such as a human within the period of a week before to a week after the administration of a medicament or combination treatment comprising AZD2171 and one of: 5-FU; CPT-11; and 5-FU and CPT-11. This means that AZD2171, 5-FU, CPT-11 and ionising radiation may be administered separately or sequentially in any order, or may be administered simultaneously. The warm-blooded animal may experience the effect of each of AZD2171, 5-FU, CPT-11 and radiation simultaneously.

According to one aspect of the present invention the ionising radiation is administered before one of AZD2171 and one of: 5-FU; CPT-11; and 5-FU and CPT-11, or after one of AZD2171 and one of: 5-FU; CPT-11; and 5-FU and CPT-11.

According to one aspect of the present invention the ionising radiation is administered before any of AZD2171 and one of: 5-FU; CPT-11; and 5-FU and CPT-11 or after all of AZD2171 and one of: 5-FU; CPT-11; and 5-FU and CPT-11.

According to one aspect of the present invention AZD2171 is administered to a warm-blooded animal after the animal has been treated with ionising radiation.

As stated above the combination treatments of the present invention, that is AZD2171, optionally with ionising radiation, combined with one of: 5-FU; CPT-11; and 5-FU and CPT-11, as defined herein, are of interest for their antiangiogenic and/or vascular permeability effects. Angiogenesis and/or increased vascular permeability is present in a wide range of

disease states including cancer (including leukaemia, multiple myeloma and lymphoma), diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, lymphoedema, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation (including age-related macular degeneration). Combination treatments of the present invention are expected to be particularly useful in the prophylaxis and treatment of diseases such as cancer and Kaposi's sarcoma. In particular combination treatments of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such combination treatments of the invention are expected to inhibit any form of cancer associated with VEGF including leukaemia, multiple myeloma and lymphoma and also, for example, to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

According to one aspect of the present invention such combination treatments of the invention are expected to slow advantageously the growth of primary and secondary (recurrent) tumours in colorectal cancer.

In another aspect of the present invention AZD2171, optionally with ionising radiation, and one of: 5-FU; CPT-11; and 5-FU and CPT-11 are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF especially those tumours which are significantly dependent on VEGF for their growth and spread.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be at least equivalent to the addition of the effects of each of the components of said treatment used alone, that is, of each of AZD2171, 5-FU, CPT-11 and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be greater than the addition of the effects of each of the components of said treatment used alone, that is, of each of AZD2171, 5-FU, CPT-11 and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be a synergistic effect.

According to the present invention a combination treatment is defined as affording a synergistic effect if the effect is therapeutically superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with AZD2171, 5-FU, CPT-11, 5-FU and CPT-11, or ionising radiation used alone. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to AZD2171, 5-FU, CPT-11, 5-FU and CPT-11, or ionising radiation used alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component(s) is/are dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of AZD2171, 5-FU, CPT-11, 5-FU and CPT-11, or ionising radiation may be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

The compositions described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for nasal administration or administration by inhalation, for example as a powder or solution, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream, for rectal administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In other embodiments of the present invention the AZD2171 of the combination treatment may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, intraperitoneally or intratumourally. Preferably AZD2171 is administered orally. In general the compositions described herein may be prepared in a conventional manner using

conventional excipients. The compositions of the present invention are advantageously presented in unit dosage form.

AZD2171 will normally be administered to a warm-blooded animal at a unit dose within the range 1-50mg per square metre body area of the animal, for example approximately 0.03-1.5 mg/kg in a human. A unit dose in the range, for example, 0.01-1.5mg/kg, preferably 0.03-0.5mg/kg is envisaged and this is normally a therapeutically-effective dose. A unit dosage form such as a tablet or capsule will usually contain, for example 1-50mg of active ingredient. Preferably a daily dose in the range of 0.03-0.5mg/kg is employed.

CPT-11 is also known as irinotecan. CPT-11 may be administered in accordance with any known route of administration and dosage.

For example CPT-11 may be dosed at 350mg/m^2 as an intravenous infusion over a 30 to 90 minute period every 3 weeks.

CPT-11 is a semi-synthetic derivative of camptothecin and is metabolised *in vivo* to an active metabolite SN-38.

5-FU is 5-fluorouracil. 5-FU may be administered according to any known route of administration and dosage.

For example 5-FU may be given as an intravenous daily infusion of 15mg/kg diluted in 500ml of 5% dextrose solution or 500ml 0.9% sodium chloride solution given by intravenous infusion: at the rate of 40 drops per minute over 4 hours; or infused over 30 to 60 minutes; or as a daily continuous infusion over 24 hours. The daily dose of 5-FU is recommended not to exceed 1g. 5-FU is usually given daily in one of these ways until 12-15g has been given and this constitutes one course of 5-FU. It is usual practice to leave 4 to 6 weeks between courses of 5-FU. Alternatively 5-FU may be dosed by intravenous injection at a dose of 12mg/kg on three consecutive days, followed by 6mg/kg on days 5, 7 and 9 ie on the three following alternate days, followed by a maintenance dose of 5-15mg/kg by intravenous injection once a week. Alternatively 5-FU may be given by intravenous injection at a dose of 15mg/kg once a week for the duration of the patient's treatment. 5-FU may also be dosed intra-arterially as a regional perfusion at 5-7.5mg/kg by 24 hour continuous infusion. 5-FU may also be dosed orally at a dose of 15mg/kg once a week or at a dose of 15mg/kg for six successive days followed by 15mg/kg once a week.

5-FU is commonly administered with leucovorin. For the avoidance of doubt the combination treatments of the present invention include the use of 5-FU when given with, or without, leucovorin.

Leucovorin may be administered according to any known route of administration and dosage. For example leucovorin may be administered orally. When used in combination with 5-FU, leucovorin is conveniently administered as calcium leucovorin and given intravenously. For example, calcium leucovorin may be given at a dose of 200mg/m^2 by slow intravenous injection, followed immediately by 5-FU at an initial dose of 370mg/m^2 by intravenous injection. The injection of leucovorin should not be given more rapidly than over 3-5 minutes because of the calcium content of the solution. This treatment is repeated daily for 5 consecutive days. Subsequent courses may be given after a treatment-free interval of 21-28 days.

Alternatively the following regimen may be used: leucovorin 500 mg/m^2 given by 2 hour infusion every week for 6 weeks with 5-FU 500 mg/m^2 given as an iv bolus midway through the 6-week period.

Alternatively the following regimen may be used: leucovorin 200 mg/m^2 given by iv 2 hour infusion followed by 5-FU 400 mg/m^2 iv bolus followed by 5-FU 600 mg/m^2 given by iv 22 hour infusion, repeated for 2 consecutive days. The cycle is repeated every 2 weeks.

Alternatively 5-FU may be administered orally as capecitabine (Xeloda^{TM}), tegafur, or TS-1. Capecitabine is a relatively non-cytotoxic fluoropyrimidine carbamate which functions as an orally administered precursor of 5-FU. Capecitabine may be administered according to any known dosage. For example a dose of 1250 mg/m^2 may be given orally twice a day, (equivalent to a daily dose of 2500mg/m^2), for 14 days followed by a rest period of 7 days.

Combination treatments of the present invention include the use of 5-FU when given in any form, (including prodrug and precursor forms that are converted to 5-FU systemically or within the tumour), when administered via any route and when given with, or without, leucovorin.

Combination treatments of the present invention include the use of CPT-11 or SN-38 when given in any form, (including prodrug and precursor forms that are converted to SN-38 systemically or within the tumour and including liposomal formulations), when administered via any route.

Radiotherapy may be administered according to the known practices in clinical radiotherapy. The dosages of ionising radiation will be those known for use in clinical radiotherapy. The radiation therapy used will include for example the use of γ-rays, X-rays, and/or the directed delivery of radiation from radioisotopes. Other forms of DNA damaging factors are also included in the present invention such as microwaves and UV-irradiation. For example X-rays may be dosed in daily doses of 1.8-2.0Gy, 5 days a week for 5-6 weeks. Normally a total fractionated dose will lie in the range 45-60Gy. Single larger doses, for example 5-10Gy may be administered as part of a course of radiotherapy. Single doses may be administered intraoperatively. Hyperfractionated radiotherapy may be used whereby small doses of X-rays are administered regularly over a period of time, for example 0.1Gy per hour over a number of days. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and on the uptake by cells.

The size of the dose of each therapy which is required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatments in order to reduce toxicity.

The combination treatments of the present invention comprise: AZD2171 and 5-FU; AZD2171 and CPT-11; AZD2171, 5-FU and CPT-11; AZD2171, 5-FU and ionising radiation; AZD2171, CPT-11 and ionising radiation; AZD2171, 5-FU, CPT-11 and ionising radiation. The agents therein may be administered separately or sequentially in any order, or may be administered simultaneously.

The present invention comprises combinations of 5-FU or CPT-11 or 5-FU and CPT-11 with AZD2171 or with a salt of AZD2171.

Salts of AZD2171 for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of AZD2171 and its pharmaceutically acceptable salts. Pharmaceutically acceptable salts may, for example, include acid addition salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition pharmaceutically acceptable salts may be formed with an inorganic or organic base which

affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt and an alkaline earth metal salt such as a calcium or magnesium salt.

AZD2171 may be synthesised according to the processes described in WO 00/47212, in particular those described in Example 240 of WO 00/47212.

The following tests may be used to demonstrate the activity of AZD2171 in combination with 5-FU and CPT-11.

Human LS-174T colon tumour xenografts in *Nude* mice

10^7 LS-174T tumour cells were injected subcutaneously (s.c.) into the flanks of athymic (*nu/nu* genotype, Swiss) mice. When tumors reached a volume of 100 to 200 mm^3 (10 days after the graft), mice were randomized into groups (15 per group) and treatment started.

(a) 5-FU + AZD2171

- The control group (Group 1) received a daily oral (p.o.) administration of AZD2171 vehicle for 14 consecutive days (day 0 – 13).
- For Group 2, the treatment consisted of a daily p.o. administration of AZD2171 alone at 3 mg/kg/adminstration for 14 consecutive days (day 0 – 13). AZD2171 was prepared as a suspension in 1% polysorbate 80 (i.e. a 1% (v/v) solution of polyoxyethylene (20) sorbitan mono-oleate in deionised water).
- For Group 3, the treatment consisted of a daily p.o. administration of AZD2171 alone at 1.5mg/kg/adminstration for 14 consecutive days (day 0 – 13). AZD2171 was prepared as a suspension in 1% polysorbate 80 (i.e. a 1% (v/v) solution of polyoxyethylene (20) sorbitan mono-oleate in deionised water).
- Group 4 received daily p.o. administration of AZD2171 at 3mg/kg/adminstration for 14 consecutive days (day 0 – 13) combined with two i.v. injections of 5-FU at 50mg/kg/injection, on day 0 and 7.
- Group 5 received daily p.o. administration of AZD2171 at 1.5mg/kg/adminstration for 14 consecutive days (day 0 – 13) combined with two i.v. injections of 5-FU at 50mg/kg/injection, on day 0 and 7.
- Group 6 received two i.v. injections of 5-FU at 50mg/kg/injection, on day 0 and 7.

The administration volume of AZD2171 was 10.0 ml/kg (200 μl for a 20 g mouse). The injection volume of 5-FU was 10.0 ml/kg (200 μl for a 20 g mouse). On days where animals

received both AZD2171 and 5-FU the 5-FU was administered 2 hours after oral dosing with AZD2171.

Group	Treatments	Combined drug doses (mg base/kg/inj.)	Adm. route	No. Treatments	No. Treatment /day	Days-interval between treatment (Days)
1	Vehicle of AZD2171	0.0	p.o.	14 p.o.	1 p.o.	1
2	AZD2171	3	p.o.	14 p.o.	1 p.o.	1
3	AZD2171	1.5	p.o.	14 p.o.	1 p.o.	1
4	AZD2171 + 5-FU	3 for AZD2171 50 for 5-FU	p.o. for AZD2171 i.v. for 5-FU	14 p.o. 2 i.v.	1 p.o. 1 i.v.	1 for p.o. 7 for i.v.
5	AZD2171 + 5-FU	1.5 for AZD2171 50 for 5-FU	p.o. for AZD2171 i.v. for 5-FU	14 p.o. 2 i.v.	1 p.o. 1 i.v.	1 for p.o. 7 for i.v.
6	5-FU	50	i.v.	2 i.v.	1 i.v.	7

Tumor volumes (mm^3) were assessed at least twice weekly by bilateral Vernier caliper measurement and, taking length to be the longest diameter across the tumor and width the corresponding perpendicular, calculated using the formula ($\pi/6$) x (length x width) x the square root of (length x width). Growth inhibition from the start of treatment was assessed by comparison of the differences in tumor volume between control and treated groups. Additionally, the effects of combination treatment are assessed by comparing tumor growth in the group of animals receiving 5-FU plus AZD2171 with the tumor growth in the groups where animals received single agent therapy alone.

The data for combination studies for AZD2171 and 5-FU, wherein AZD2171 was dosed at 3 or 1.5mg/kg is shown in Figures 1 and 2. Statistical significance was evaluated using a one-tailed two-sample t-test.

The combination of 5-FU with AZD2171 dosed at 3mg/kg produced a significantly greater inhibition of tumour growth than 5-FU alone or AZD2171 alone (Figure 1). The inhibition of tumour growth produced by the combination of the two agents AZD2171 and 5-FU was still greater than that produced by either agent alone when the dose of AZD2171 was reduced to 1.5mg/kg (Figure 2).

(b) CPT-11 + AZD2171

- The control group (Group 1) received a daily oral (p.o.) administration of AZD2171 vehicle for 14 consecutive days (day 0 – 13).
- For Group 2, the treatment consisted of a daily p.o. administration of AZD2171 alone at 3mg/kg/adminstration for 14 consecutive days (day 0 – 13). AZD2171 was prepared as a suspension in 1% polysorbate 80 (i.e. a 1% (v/v) solution of polyoxyethylene (20) sorbitan mono-oleate in deionised water).
- For Group 3, the treatment consisted of a daily p.o. administration of AZD2171 alone at 1.5mg/kg/adminstration for 14 consecutive days (day 0 – 13). AZD2171 was prepared as a suspension in 1% polysorbate 80 (i.e. a 1% (v/v) solution of polyoxyethylene (20) sorbitan mono-oleate in deionised water).
- Group 4 received daily p.o. administration of AZD2171 at 3mg/kg/adminstration for 14 consecutive days (day 0 – 13) combined with two i.v. injections of CPT-11 at 25mg/kg/injection, on day 0 and 7.
- Group 5 received daily p.o. administration of AZD2171 at 1.5mg/kg/adminstration for 14 consecutive days (day 0 – 13) combined with two i.v. injections of CPT-11 at 25mg/kg/injection, on day 0 and 7.
- Group 6 received two i.v. injections of CPT-11 at 25mg/kg/injection, on day 0 and 7.

The administration volume of AZD2171 was 10.0 ml/kg (200 μl for a 20 g mouse). The injection volume of CPT-11 was 10.0 ml/kg (200 μl for a 20 g mouse). On days where animals received both AZD2171 and CPT-11 the CPT-11 was administered 2 hours after oral dosing with AZD2171.

Group	Treatments	Combined drug doses (mg base/kg/inj.)	Adm. route	No. Treatments	No. Treatment /day	Days-interval between treatment (Days)
1	Vehicle of AZD2171	0.0	p.o.	14 p.o.	1 p.o.	1 for p.o.
2	AZD2171	3	p.o.	14 p.o.	1 p.o.	1 for p.o.
3	AZD2171	1.5	p.o.	14 p.o.	1 p.o.	1 for p.o.
4	AZD2171 + CPT-11	3 for AZD2171 25.0 for CPT-11	p.o. for AZD2171 i.v. for CPT-11	14 p.o. 2 i.v.	1 p.o. 1 i.v.	1 for p.o. 7 for i.v.
5	AZD2171 + CPT-11	3 for AZD2171 25.0 for CPT-11	p.o. for AZD2171 i.v. for CPT-11	14 p.o. 2 i.v.	1 p.o. 1 i.v.	1 for p.o. 7 for i.v.
6	CPT-11	25.0	i.v.	2 i.v.	1 i.v.	7 for i.v.

Tumor volumes (mm^3) were assessed at least twice weekly by bilateral Vernier caliper measurement and, taking length to be the longest diameter across the tumor and width the corresponding perpendicular, calculated using the formula ($\pi/6$) x (length x width) x square root of (length x width). Growth inhibition from the start of treatment was assessed by comparison of the differences in tumor volume between control and treated groups. Additionally, the effects of combination treatment are assessed by comparing tumor growth in the group of animals receiving CPT-11 plus AZD2171 with the tumor growth in the groups where animals received single agent therapy alone.

The data for combination studies for AZD2171 and CPT-11, wherein AZD2171 was dosed at 3 or 1.5mg/kg is shown in Figures 3 and 4.

Statistical significance was evaluated using a one-tailed two-sample t-test.

The combination of CPT-11 with AZD2171 dosed at 3mg/kg or 1.5mg/kg produced a significantly greater inhibition of tumour growth than CPT-11 alone or AZD2171 alone (Figures 3 and 4).

An analogous experiment may be used to look at the combination of AZD2171, 5-FU and CPT-11 in this animal model.

An analogous experiment may be used to look at the combination of AZD2171, 5-FU, CPT-11 and ionising radiation in this animal model.

CLAIMS

1. Use of AZD2171 or a pharmaceutically acceptable salt thereof and one of:
   a) 5-FU;
   b) CPT-11; and
   c) 5-FU and CPT-11

in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

2. Use of AZD2171 or a pharmaceutically acceptable salt thereof and one of:
   a) 5-FU;
   b) CPT-11; and
   c) 5-FU and CPT-11

in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

3. Use of AZD2171 or a pharmaceutically acceptable salt thereof and one of:
   a) 5-FU;
   b) CPT-11; and
   c) 5-FU and CPT-11

in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

4. Use of AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

5. Use of AZD2171 or a pharmaceutically acceptable salt thereof and CPT-11 in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

6. Use of AZD2171 or a pharmaceutically acceptable salt thereof and 5-FU and CPT-11 in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

7. Use according to any one of claims 2, 4, 5 and 6 wherein the cancer is colorectal cancer.

8. A pharmaceutical composition comprising AZD2171 or a pharmaceutically acceptable salt thereof, and 5-FU in association with a pharmaceutically acceptable excipient or carrier.

9. A pharmaceutical composition comprising AZD2171 or a pharmaceutically acceptable salt thereof, and CPT-11 in association with a pharmaceutically acceptable excipient or carrier.

10. A pharmaceutical composition comprising AZD2171 or a pharmaceutically acceptable salt thereof, and 5-FU and CPT-11 in association with a pharmaceutically acceptable excipient or carrier.

11. A kit comprising AZD2171 or a pharmaceutically acceptable salt thereof, and 5-FU.

12. A kit comprising AZD2171 or a pharmaceutically acceptable salt thereof, and CPT-11.

13. A kit comprising AZD2171 or a pharmaceutically acceptable salt thereof, and 5-FU and CPT-11.

14. A method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of one of:

a) 5-FU;

b) CPT-11; and

c) 5-FU and CPT-11.

15. A method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of AZD2171 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of one of:

d) 5-FU;

e) CPT-11; and

f) 5-FU and CPT-11;

and before, after or simultaneously with an effective amount of ionising radiation.

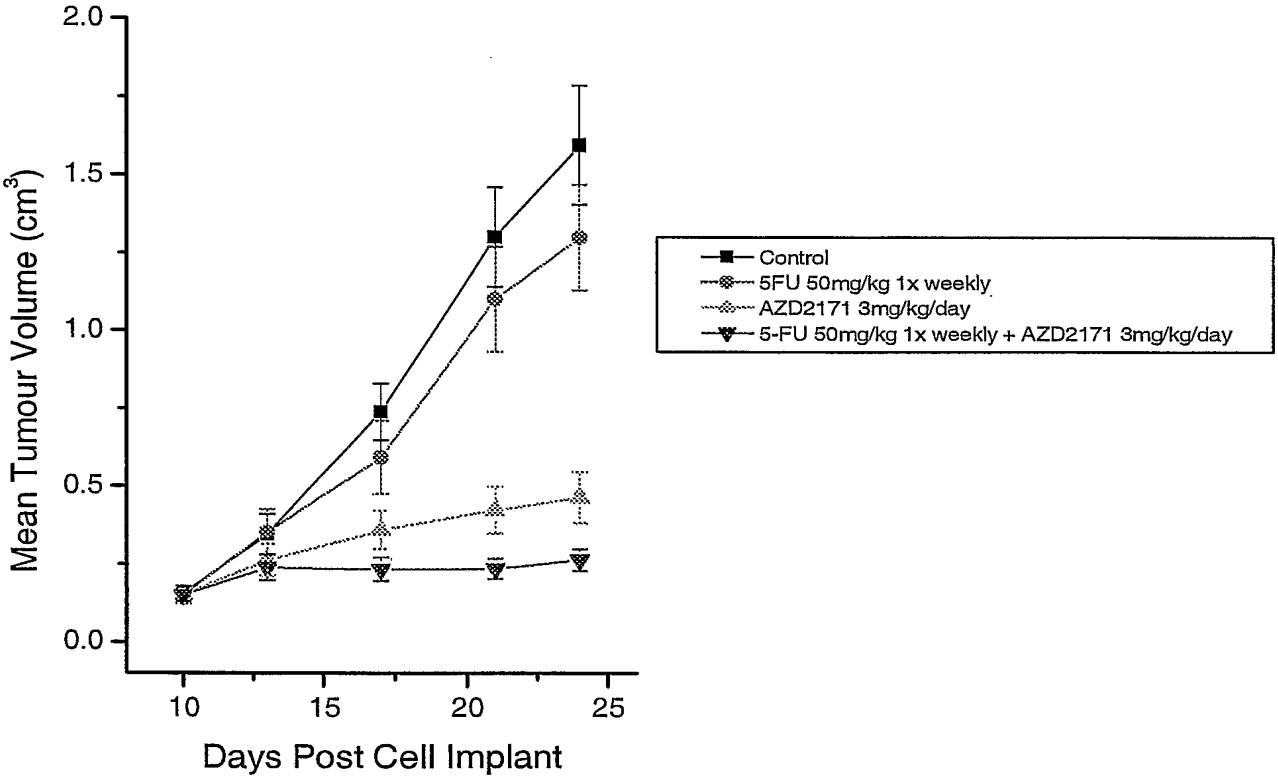


Figure 1

5-FU 50/kg vs 5-FU 50mg/kg + AZD2171 3mg/kg $p<0.001$

AZD2171 3mg/kg vs 5-FU 50mg/kg + AZD2171 3mg/kg $p<0.05$

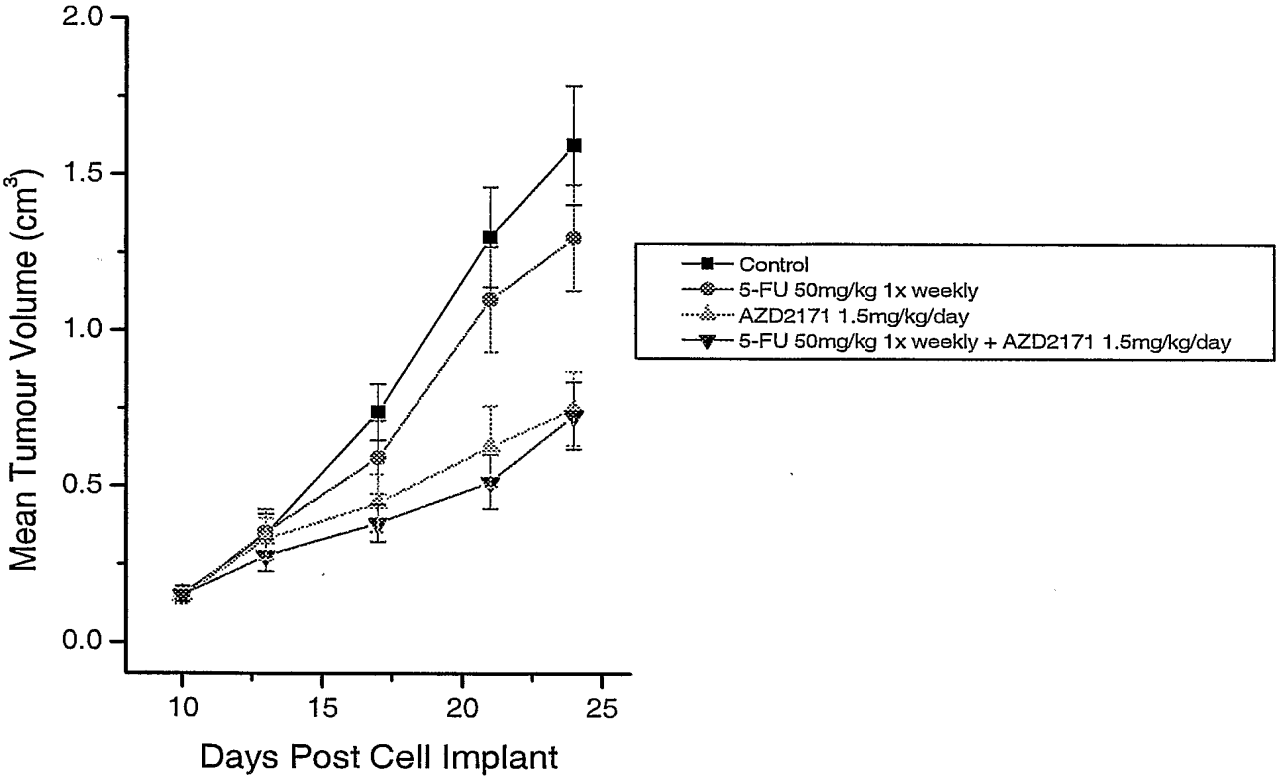


Figure 2

5-FU 50/kg vs 5-FU 50mg/kg + AZD2171 1.5mg/kg	$p<0.001$
AZD2171 1.5mg/kg vs 5-FU 50mg/kg + AZD2171 1.5mg/kg	$p=0.4$

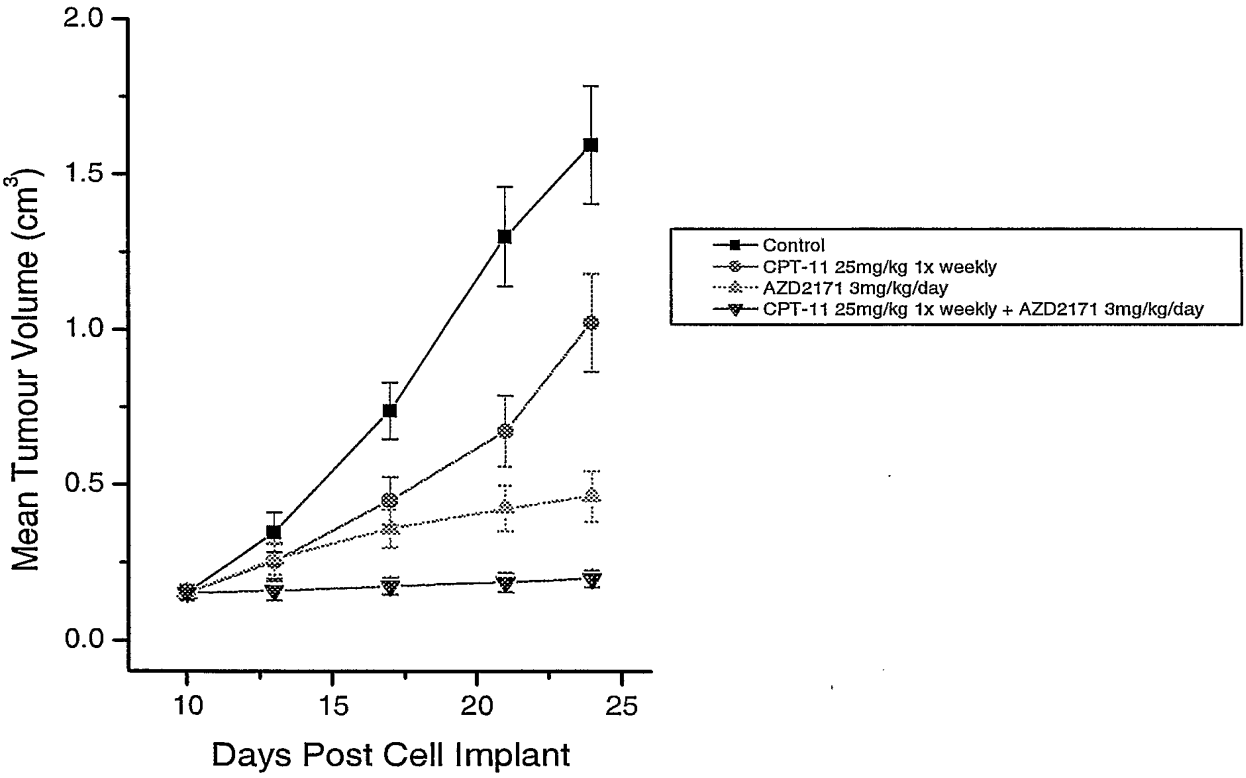


Figure 3

CPT-11 25mg/kg vs CPT-11 25mg/kg + AZD2171 3 mg/kg	$p<0.001$
AZD2171 3mg/kg vs CPT-11 25mg/kg + AZD2171 3mg/kg	$p<0.001$

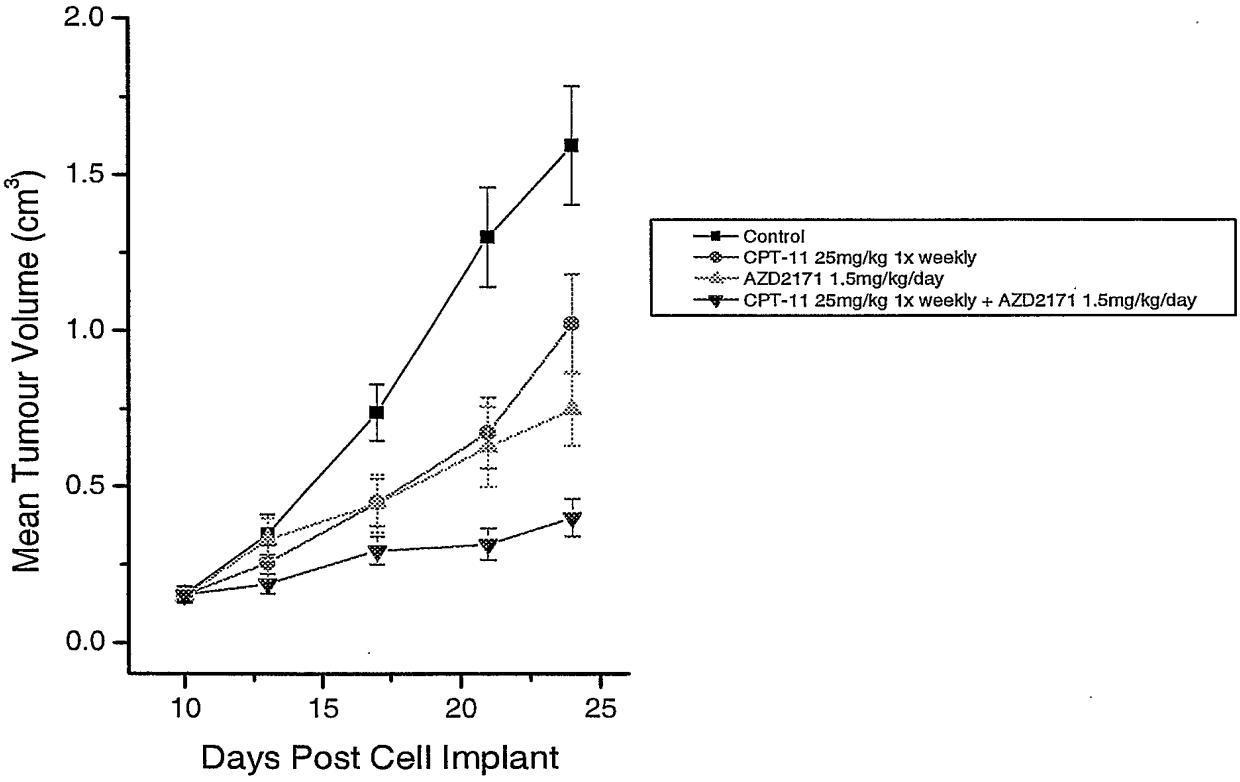


Figure 4

CPT-11 25mg/kg vs CPT-11 25mg/kg + AZD2171 1.5mg/kg $p<0.001$

AZD2171 1.5mg/kg vs CPT-11 25mg/kg + AZD2171 1.5mg/kg $p<0.05$